



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07D 211/90 | A1 | (11) International Publication Number: WO 99/52873 (43) International Publication Date: 21 October 1999 (21.10.99) |
| (21) International Application Number: PCT/PL99/00011 (22) International Filing Date: 8 April 1999 (08.04.99) (30) Priority Data: P.325757 9 April 1998 (09.04.98) PL (71) Applicant: ADAMED SP. Z O.O. [PL/PL]; Pieńków 149, PL-05-152 Czosnów k/Warszawy (PL). (72) Inventors: WŁOSTOWSKI, Marek; ul. Siemiatycka 1/60, PL-01-312 Warszawa (PL). WIECZOREK, Maciej; ul. Gamcarska 23, PL-27-400 Ostrowiec Świętokrzyski (PL). (74) Agent: SITKOWSKA, Jadwiga; Patpol Ltd., ul. Nowoursyn- owska 162J, PL-02-766 Warszawa (PL). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: A PROCESS FOR THE PREPARATION OF AMLODIPINE BENZENESULPHONATE | | |
| <div style="text-align: center;"> </div> | | |
| (57) Abstract <p>A process for the preparation of amlodipine benzenesulphonate is disclosed, wherein a salt of amlodipine with an inorganic or organic acid is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C₁-C₂. Amlodipine benzenesulphonate is used for the preparation of a medicament having calcium channel blocking activity, useful in the treatment of the coronary disease and arterial hypertension.</p> | | |

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A process for the preparation of amlodipine
benzenesulphonate

The present invention relates to a process for the
10 preparation of amlodipine benzenesulphonate, i.e. 2-(2-
aminoethoxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-
methoxycarbonyl-6-methyl-1,4-dihydropyridine
monobenzenesulphonate of the formula I as presented on the
annexed drawing.

15 Amlodipine is a modern medicament belonging to the
group of calcium channel blockers. It has a significant
selectivity against resistance arterioles and coronary
arteries and specific pharmacokinetic properties: good
bioavailability, long half-life, slow onset and decline of
20 action onset as well as long-lasting pharmacological
reaction, any substantial interactions with other
medicaments being absent.

Due to these advantages amlodipine is utilized
successfully in the treatment of arterial hypertension as a
25 first choice therapeutic agent; it is also used
successfully in the treatment of coronary disease,
including Prinzmetal angina and other circulatory system
diseases.

While amlodipine shows biological activity in its free base form, it is used in the pharmaceutical preparations as a salt with pharmacologically acceptable acids.

The European Patent Application EP 089,167 discloses a series of pharmaceutically acceptable amlodipine salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, maleate, tartrate, citrate and others. Maleate is indicated as the most preferred salt.

The European Patent Application EP 0244944 discloses the process for the preparation of amlodipine benzenesulphonate, which comprises treating amlodipine as a free base with benzenesulphonic acid or alternatively with benzenesulphonic acid ammonium salt in an inert organic solvent. In the examples of realisation (Examples I and V) industrial methyl alcohol is used as a solvent.

Amlodipine benzenesulphonate has been accepted for amlodipine administration both in the form of tablets and sterile aqueous solutions.

Amlodipine benzenesulphonate shows certain physical properties making it particularly destined for a pharmaceutically acceptable amlodipine salt. It is much more stable than other salts both as a solid and a solution; it is relatively well soluble in water (4.6 mg/ml) but not hygroscopic. The pH of a saturated aqueous solution is about 6.6 being relatively close to the blood pH 7.4. Finally, due to its excellent mechanical properties can be easily compressed, forming tablets of a good quality without adhering to the punch of the tableting machine, etc.

However, while amlodipine benzenesulphonate excellently meets the requirements for a good pharmaceutical material, the known process for preparing thereof has some disadvantages.

5 The process for the preparation of amlodipine benzenesulphonate according to EP 0244 944 comprises reacting free base of amlodipine with benzenesulphonic acid. The process is performed in an alcohol and thus may cause some fire hazard due to alcohol inflammability. The
10 additional disadvantage is due to the fact that the reaction utilizes the free benzenesulphonic acid, which is a caustic, corroding and noxious substance. Additionally, due to its high hygroscopicity the acid requires the special safeguards during transport and handling and in
15 practice is used in the form of dense oily material containing about 90% of acid and about 10% of water.

The alternative process also presents some hazards. Although the dangerous benzenesulphonic acid has been replaced with its ammonium salt, thus eliminating hazards
20 and drawbacks connected with the use of free acid, the formation of amlodipine benzenesulphonate is accompanied, however, with the evolution of gaseous ammonia which is toxic and dangerous and has to be additionally absorbed and deactivated. Of course, the fire hazard connected with an
25 inflammable alcohol is still present.

The above-discussed hazards and difficulties are eliminated by the process for the preparation of amlodipine benzenesulphonate of the present invention.

According to the process of the present invention,
30 amlodipine salt with an inorganic or organic acid (with the

exception of salt with benzenesulphonic acid) is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C₁-C₂.

Preferably the amlodipine salt selected from acetate, 5 formate, chloroacetate, hydrobromide, nitrate, hydrochloride, methanesulphonate is used. Especially preferred are hydrochloride, acetate or formate.

Alkali metal benzenesulphonate comprises lithium, sodium and potassium benzenesulphonate. Particularly 10 preferred is sodium benzenesulphonate as an inexpensive, safe, stable and commercially available chemical product.

Preferred water-alcohol mixture is the mixture water-ethanol, comprising from 20 to 50% (v/v) of ethanol, especially 1:1 mixture.

15 The process of the invention may be realised by preparing a solution or a suspension of amlodipine salt in water or a water-alcohol mixture, and adding, preferably at 5-40°C with vigorous stirring, a solution of sodium benzenesulphonate in water in a stoichiometric amount or 20 preferably at a molar ratio of sodium benzenesulphonate/amlodipine salt being 1:1.15. The mixture is stirred for about 10-60 minutes, optionally warmed to 40°C and then cooled to 10°C. The resulting precipitate of amlodipine benzenesulphonate is filtered off, washed twice with water 25 and dried. If the salt separates as an oil, it is necessary to add some amlodipine benzenesulphonate crystals to speed the crystallization process. The product thus obtained contains no contaminants. Alternatively, the process can be performed by adding solid sodium benzenesulphonate to the 30 amlodipine salt. The reverse order of reagents addition,

i.e. adding the amlodipine salt to the solution of sodium benzenesulphonate in water also results in a highly pure product.

The following non-limiting Examples are presented
5 below to illustrate the invention:

Example 1

To the water (150 ml) amlodipine hydrochloride (71.5 g) was added and the mixture was stirred for 15 minutes at 20°C. The solution of sodium benzenesulphonate
10 (33.3 g) in 200 ml of water was added portionwise during 10 minutes. A small amount of amlodipine benzenesulphonate crystals as seeds for crystallization was added and the mixture was stirred for 40 minutes. It was then cooled to 10°C and the resulting precipitate filtered off. The
15 precipitate was washed with distilled water (3x 100 ml) and dried. 80.0 g of amlodipine benzenesulphonate was obtained, mp=201°C. Yield: 88%.

Example 2

To the solution of sodium benzenesulphonate (4 g) in
20 water (20 ml) amlodipine formate (9.1 g) was added portionwise with stirring at 20°C. After addition had been completed, the mixture was stirred for 20 minutes, then cooled to 5°C and the product precipitate filtered off. The precipitate was washed with water (2 x 20 ml) and dried in
25 vacuo. 18.8 g of amlodipine benzenesulphonate was obtained, mp=201°C. Yield: 90%.

Example 3

To the solution of amlodipine hydrobromide (9.6 g) in water (25 ml) sodium benzenesulphonate (4 g) was added
30 portionwise with vigorous stirring. After addition had been

completed, the mixture was stirred for 20 minutes, then cooled to 5°C, and following the procedure of Example 2 11.6 g of amlodipine benzenesulphonate was obtained, mp=201°C.

5 Example 4

To the solution of sodium benzenesulphonate (4 g) in water (10 ml) amlodipine acetate (9.3 g) in 20 ml of the water-ethanol mixture (1:1) was added portionwise with stirring at 20°C. After addition had been completed, the
10 mixture was stirred for 30 minutes, then cooled to 5°C, and several crystals of amlodipine benzenesulphonate and additionally 10 ml of water were added. Following the procedure of Example 2 amlodipine benzenesulphonate was obtained with the yield of 83%, mp=201°C.

15 Example 5

Starting from amlodipine chloroacetate (10.6 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 89% yield, mp=201°C.

20 Example 6

Starting from amlodipine methanesulphonate (10.6 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 81% yield, mp=201°C.

25 Example 6

Starting from amlodipine nitrate (9.4 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 83% yield, mp=201°C.

Claims

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1. A process for the preparation of amlodipine benzenesulphonate of the Formula I, characterised in that a salt of amlodipine with an inorganic or organic acid is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C₁-C₂.

2. The process according to claim 1, characterised in that the salt of amlodipine is selected from acetate, formate, chloroacetate, hydrobromide, nitrate, hydrochloride or methanesulphonate, preferably hydrochloride.

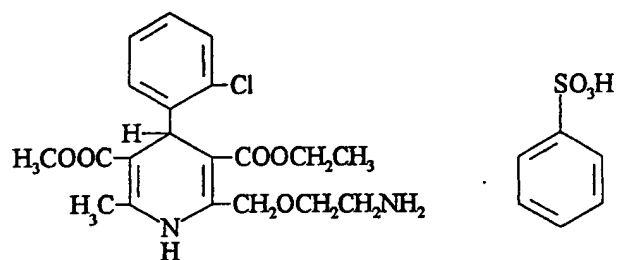
3. The process according to any one of claims 1-2, characterised in that the alkali metal benzenesulphonate is sodium benzenesulphonate.

4. The process according to any one of claims 1-3, characterised in that the reaction is performed in the water-ethanol mixture containing from 20 to 50% of ethanol, especially 1:1 mixture.

5. The process according to any one of claims 1-4, characterised in that the reaction is performed in the aqueous medium.

6. The process according to claim any one of claims 1-5, characterised in that the reaction is performed at the temperature 5-40°C.

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Formula I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/PL 99/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | EP 0 244 944 A (PFIZER LTD) 11 November 1987 (1987-11-11) cited in the application the whole document; in particular, page 9, lines 1-7 ----- | 1-6 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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